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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A  
FILING DATE.

APPLICATION NUMBER: 60/400,356

FILING DATE: July 31, 2002

RELATED PCT APPLICATION NUMBER: PCT/US03/23820



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08-02-02 40035 073102 A/Prov

PTO/SB/16 (10-01)

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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.63 (c).

Express Mail Label No. EU465991597US

INVENTOR(S)				
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)		
GARY DAVID	ANNIS	LANDENBERG, PENNSYLVANIA		
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto				
TITLE OF THE INVENTION (500 characters max)				
METHOD FOR PREPARING 3-HALO-4,5-DIHYDRO-1H-PYRAZOLES				
Direct all correspondence to: CORRESPONDENCE ADDRESS				
<input checked="" type="checkbox"/> Customer Number OR		23906 Type Customer Number Here		 PATENT TRADEMARK OFFICE
<input type="checkbox"/> Firm or Individual Name				
Address				
Address				
City	State	ZIP		
Country	Telephone	Fax		
ENCLOSED APPLICATION PARTS (check all that apply)				
<input checked="" type="checkbox"/> Specification Number of Pages		31	<input type="checkbox"/> CD(s), Number	
<input type="checkbox"/> Drawing(s) Number of Sheets			<input type="checkbox"/> Other (specify)	
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76		Return Receipt Postcard		
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT				
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.				
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees				
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:		04-1928	FILING FEE AMOUNT (\$) 160.00	
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.				
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.				
<input checked="" type="checkbox"/> No.				
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____				

Respectfully submitted,

Date 07/31/02

SIGNATURE

David E Heiser

TYPED or PRINTED NAME DAVID E. HEISER

TELEPHONE 302-892-1926

REGISTRATION NO. 31,366

(If appropriate)

Docket Number

BA9307 US PRV

## USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

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**FEE TRANSMITTAL  
for FY 2002**

Patent fees are subject to annual revision.

☐ Applicant Claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT** (\$) 160**Complete if Known**

Application Number	UNKNOWN
Filing Date	CONCURRENTLY HEREWITH
First Named Inventor	GARY DAVID ANNIS
Examiner Name	UNKNOWN
Group / Art Unit	UNKNOWN
Attorney Docket No.	BA9307 US PRV

**METHOD OF PAYMENT (check all that apply)**☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit AccountDeposit  
Account  
Number  
**04-1928**Deposit  
Account  
Name  
**E. I. du Pont de Nemours and Company**

The Commissioner is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments  
☒ Charge any additional fee(s) during the pendency of this application  
☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account
**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	160
<b>SUBTOTAL (1)</b>					<b>(\$)</b> 160

**2. EXTRA CLAIM FEES**

Total Claims	-20	=	0	X	18	=	0
Independent Claims	-3	=	0	X	84	=	0
Multiple Dependent				X	280	=	0

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
103	18	203	9	Claims in excess of 20	
102	84	202	42	Independent claims in excess of 3	
104	280	204	140	Multiple dependent claim, if not paid	
109	84	209	42	** Reissue Independent claims over original patent	
110	18	210	9	** Reissue claims in excess of 20 and over original patent	
<b>SUBTOTAL (2)</b>					<b>(\$)</b> 0

\*\*or number previously paid, if greater; For Reissues, see above

**FEE CALCULATION (continued)****3. ADDITIONAL FEES**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) \_\_\_\_\_

\*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** (\$) 0**SUBMITTED BY****Complete (if applicable)**

Name (Print/Type)	DAVID E HEISER	Registration No. Attorney/Agent)	31, 366	Telephone	302-892-1928
Signature	<i>David E Heiser</i>	Date	JULY 31, 2002		

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Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

TITLE

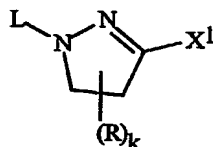
## METHOD FOR PREPARING 3-HALO-4,5-DIHYDRO-1H-PYRAZOLES

BACKGROUND OF THE INVENTION

- A need exists for additional methods to prepare 3-halo-4,5-dihydro-1H-pyrazoles.
- 5 Such compounds include useful intermediates for the preparation of crop protection agents, pharmaceuticals and other fine chemicals.

SUMMARY OF THE INVENTION

This invention relates to a method for preparing a 3-halo-4,5-dihydro-1H-pyrazole compound of Formula I



10

I

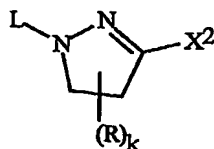
wherein L is an optionally substituted carbon moiety;

each R is independently selected from optionally substituted carbon moieties;

k is an integer from 0 to 4;

and X<sup>1</sup> is halogen.

- 15 The method comprises contacting a 4,5-dihydro-1H-pyrazole compound of Formula II



II

wherein X<sup>2</sup> is OS(O)<sub>m</sub>R<sup>1</sup>, OP(O)<sub>p</sub>(OR<sup>2</sup>)<sub>2</sub> or a halogen other than X<sup>1</sup>;

m is 1 or 2;

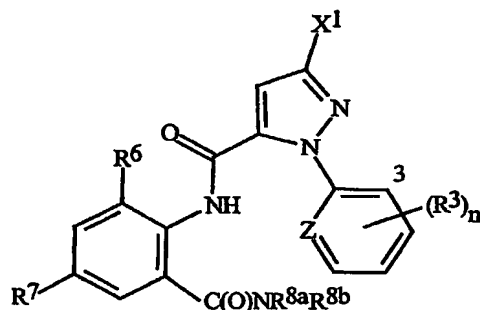
p is 0 or 1;

- 20 R<sup>1</sup> is selected from alkyl and haloalkyl; and phenyl optionally substituted with from 1 to 3 substituents selected from alkyl and halogen; and

each R<sup>2</sup> is independently selected from alkyl and haloalkyl; and phenyl optionally substituted with from 1 to 3 substituents selected from alkyl and halogen;

with a compound of the formula HX<sup>1</sup> in the presence of a suitable solvent.

This invention also relates to a method of preparing a compound of Formula III,



III

wherein

$X^1$  is halogen;

5 each  $R^3$  is independently  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_4$  alkenyl,  $C_2$ - $C_4$  alkynyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_4$  haloalkyl,  $C_2$ - $C_4$  haloalkenyl,  $C_2$ - $C_4$  haloalkynyl,  $C_3$ - $C_6$  halocycloalkyl, halogen, CN,  $NO_2$ ,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  haloalkoxy,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkylsulfinyl,  $C_1$ - $C_4$  alkylsulfonyl,  $C_1$ - $C_4$  alkylamino,  $C_2$ - $C_8$  dialkylamino,  $C_3$ - $C_6$  cycloalkylamino,  $(C_1$ - $C_4$  alkyl)( $C_3$ - $C_6$  cycloalkyl)amino,   
10  $C_2$ - $C_4$  alkylcarbonyl,  $C_2$ - $C_6$  alkoxy carbonyl,  $C_2$ - $C_6$  alkylaminocarbonyl,  $C_3$ - $C_8$  dialkylaminocarbonyl or  $C_3$ - $C_6$  trialkylsilyl;

Z is N or  $CR^5$ ;

$R^5$  is H or  $R^3$ ;

$R^6$  is  $CH_3$ , F, Cl or Br;

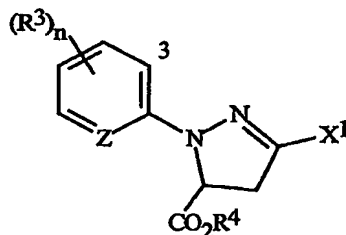
15  $R^7$  is F, Cl, Br, I or  $CF_3$ ;

$R^{8a}$  is  $C_1$ - $C_4$  alkyl;

$R^{8b}$  is H or  $CH_3$ ; and

n is an integer from 0 to 3

using a compound of Formula Ia



Ia

20 wherein  $R^4$  is H or an optionally substituted carbon moiety.

This method is characterized by preparing the compound of Formula Ia (i.e. a subgenus of Formula I) by the method as indicated above.

### DETAILED DESCRIPTION OF THE INVENTION

In the recitations herein, the term "carbon moiety" refers to a radical in which a carbon atom is connected to the backbone of the 4,5-dihydro-1*H*-pyrazole ring. As the carbon moieties L and R (including R<sup>4</sup>) are substituents separated from the reaction center, they can encompass a great variety of carbon-based groups preparable by modern methods of synthetic organic chemistry. The method of this invention is generally applicable to a wide range of starting compounds of Formula I and product compounds of Formula II. One skilled in the art will recognize that certain groups are sensitive to hydrogen halides and may be transformed under the reaction conditions. One skilled in the art will also recognize that certain groups are basic and can form salts with hydrogen halides, and thus the method of this invention can require additional hydrogen halide.

"Carbon moiety" thus includes alkyl, alkenyl and alkynyl, which can be straight-chain or branched. "Carbon moiety" also includes carbocyclic and heterocyclic rings, which can be saturated, partially saturated, or completely unsaturated. Furthermore, unsaturated rings can be aromatic if Hückel's rule is satisfied. The carbocyclic and heterocyclic rings of a carbon moiety can form polycyclic ring systems comprising multiple rings connected together. The term "carbocyclic ring" denotes a ring wherein the atoms forming the ring backbone are selected only from carbon. The term "heterocyclic ring" denotes a ring wherein at least one of the ring backbone atoms is other than carbon. "Saturated carbocyclic" refers to a ring having a backbone consisting of carbon atoms linked to one another by single bonds; unless otherwise specified, the remaining carbon valences are occupied by hydrogen atoms. The term "aromatic ring system" denotes fully unsaturated carbocycles and heterocycles in which at least one ring in a polycyclic ring system is aromatic. Aromatic indicates that each of ring atoms is essentially in the same plane and has a *p*-orbital perpendicular to the ring plane, and in which  $(4n + 2) \pi$  electrons, when *n* is 0 or a positive integer, are associated with the ring to comply with Hückel's rule. The term "aromatic carbocyclic ring system" includes fully aromatic carbocycles and carbocycles in which at least one ring of a polycyclic ring system is aromatic. The term "nonaromatic carbocyclic ring system" denotes fully saturated carbocycles as well as partially or fully unsaturated carbocycles wherein none of the rings in the ring system are aromatic. The terms "aromatic heterocyclic ring system" and "heteroaromatic ring" include fully aromatic heterocycles and heterocycles in which at least one ring of a polycyclic ring system is aromatic. The term "nonaromatic heterocyclic ring system" denotes fully saturated heterocycles as well as partially or fully unsaturated heterocycles wherein none of the rings in the ring system are aromatic. The term "aryl" denotes a carbocyclic or heterocyclic ring or ring system in which at least one ring is aromatic, and the aromatic ring provides the connection to the remainder of the molecule.

The carbon moieties specified for L, R and R<sup>4</sup> are optionally substituted. The term "optionally substituted" in connection with these carbon moieties refers to carbon moieties that are unsubstituted or have at least one non-hydrogen substituent. Illustrative optional substituents include alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, hydroxycarbonyl, formyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkoxycarbonyl, hydroxy, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, aryloxy, alkylthio, alkenylthio, alkynylthio, cycloalkylthio, arylthio, alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, cycloalkylsulfinyl, arylsulfinyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, amino, alkylamino, alkenylamino, alkynylamino, arylamino, aminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkynylaminocarbonyl, arylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkynylaminocarbonyl, arylaminocarbonyloxy, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino and aryloxy-carbonylamino, each further optionally substituted; and halogen, cyano and nitro. The optional further substituents are independently selected from groups like those illustrated above for the substituents themselves to give additional substituent groups for L, R and R<sup>4</sup> such as haloalkyl, haloalkenyl and haloalkoxy. As a further example, alkylamino can be further substituted with alkyl, giving dialkylamino. The substituents can also be tied together by figuratively removing one or two hydrogen atoms from each of two substituents or a substituent and the supporting molecular structure and joining the radicals to produce cyclic and polycyclic structures fused or appended to the molecular structure supporting the substituents. For example, tying together adjacent hydroxy and methoxy groups attached to, for example, a phenyl ring gives a fused dioxolane structure containing the linking group -O-CH<sub>2</sub>-O-. Tying together a hydroxy group and the molecular structure to which it is attached can give cyclic ethers, including epoxides. Illustrative substituents also include oxygen, which when attached to carbon forms a carbonyl function.

As referred to herein, "alkyl", used either alone or in compound words such as "alkylthio" or "haloalkyl" includes straight-chain or branched alkyl, such as, methyl, ethyl, *n*-propyl, *i*-propyl, or the different butyl, pentyl or hexyl isomers. The term "1-2 alkyl" indicates that one or two of the available positions for that substituent may be alkyl which are independently selected. "Alkenyl" includes straight-chain or branched alkenes such as ethenyl, 1-propenyl, 2-propenyl, and the different butenyl, pentenyl and hexenyl isomers. "Alkenyl" also includes polyenes such as 1,2-propadienyl and 2,4-hexadienyl. "Alkynyl" includes straight-chain or branched alkynes such as ethynyl, 1-propynyl, 2-propynyl and the different butynyl, pentynyl and hexynyl isomers. "Alkynyl" can also include moieties comprised of multiple triple bonds such as 2,5-hexadiynyl. "Alkoxy" includes, for example, methoxy, ethoxy, *n*-propyloxy, isopropyloxy and the different butoxy, pentoxy and hexyloxy isomers. "Alkenyloxy" includes straight-chain or branched alkenyloxy moieties. Examples of "alkenyloxy" include H<sub>2</sub>C=CHCH<sub>2</sub>O, (CH<sub>3</sub>)<sub>2</sub>C=CHCH<sub>2</sub>O, (CH<sub>3</sub>)CH=CHCH<sub>2</sub>O,

(CH<sub>3</sub>)CH=C(CH<sub>3</sub>)CH<sub>2</sub>O and CH<sub>2</sub>=CHCH<sub>2</sub>CH<sub>2</sub>O. "Alkynyloxy" includes straight-chain or branched alkynyloxy moieties. Examples of "alkynyloxy" include HC≡CCH<sub>2</sub>O, CH<sub>3</sub>C≡CCH<sub>2</sub>O and CH<sub>3</sub>C≡CCH<sub>2</sub>CH<sub>2</sub>O. "Alkylthio" includes branched or straight-chain alkylthio moieties such as methylthio, ethylthio, and the different propylthio, butylthio, 5 pentylthio and hexylthio isomers. "Alkylsulfinyl" includes both enantiomers of an alkylsulfinyl group. Examples of "alkylsulfinyl" include CH<sub>3</sub>S(O), CH<sub>3</sub>CH<sub>2</sub>S(O), CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>S(O), (CH<sub>3</sub>)<sub>2</sub>CHS(O) and the different butylsulfinyl, pentylsulfinyl and hexylsulfinyl isomers. Examples of "alkylsulfonyl" include CH<sub>3</sub>S(O)<sub>2</sub>, CH<sub>3</sub>CH<sub>2</sub>S(O)<sub>2</sub>, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>S(O)<sub>2</sub>, (CH<sub>3</sub>)<sub>2</sub>CHS(O)<sub>2</sub> and the different butylsulfonyl, pentylsulfonyl and 10 hexylsulfonyl isomers. "Alkylamino", "alkenylthio", "alkenylsulfinyl", "alkenylsulfonyl", "alkynylthio", "alkynylsulfinyl", "alkynylsulfonyl", and the like, are defined analogously to the above examples. Examples of "alkylcarbonyl" include C(O)CH<sub>3</sub>, C(O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and C(O)CH(CH<sub>3</sub>)<sub>2</sub>. Examples of "alkoxycarbonyl" include CH<sub>3</sub>OC(=O), CH<sub>3</sub>CH<sub>2</sub>OC(=O), CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>OC(=O), (CH<sub>3</sub>)<sub>2</sub>CHOC(=O) and the different butoxy- or pentoxycarbonyl 15 isomers. "Cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "cycloalkoxy" includes the same groups linked through an oxygen atom such as cyclopentyloxy and cyclohexyloxy. "Cycloalkylamino" means the amino nitrogen atom is attached to a cycloalkyl radical and a hydrogen atom and includes groups such as cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino. 20 "(Alkyl)(cycloalkyl)amino" means a cycloalkylamino group where the hydrogen atom is replaced by an alkyl radical; examples include groups such as (methyl)(cyclopropyl)amino, (butyl)(cyclobutyl)amino, (propyl)cyclopentylamino, (methyl)cyclohexylamino and the like. "Cycloalkenyl" includes groups such as cyclopentenyl and cyclohexenyl as well as groups with more than one double bond such as 1,3- and 1,4-cyclohexadienyl.

25 The term "halogen", either alone or in compound words such as "haloalkyl", includes fluorine, chlorine, bromine or iodine. The term "1-2 halogen" indicates that one or two of the available positions for that substituent may be halogen which are independently selected. Further, when used in compound words such as "haloalkyl", said alkyl may be partially or fully substituted with halogen atoms which may be the same or different. Examples of 30 "haloalkyl" include F<sub>3</sub>C, ClCH<sub>2</sub>, CF<sub>3</sub>CH<sub>2</sub> and CF<sub>3</sub>CCl<sub>2</sub>.

The total number of carbon atoms in a substituent group is indicated by the "C<sub>i</sub>-C<sub>j</sub>" prefix where i and j are, for example, numbers from 1 to 3; e.g., C<sub>1</sub>-C<sub>3</sub> alkyl designates methyl through propyl.

35 Although there is no definite limit to the sizes of Formulae I and II suitable for the processes of the invention, typically Formula II comprises 4-100, more commonly 4-50, and most commonly 4-25 carbon atoms, and 3-25, more commonly 3-15, and most commonly 3-10 heteroatoms. The heteroatoms are commonly selected from halogen, oxygen, sulfur, nitrogen and phosphorus. Two heteroatoms in Formulae I and II are the



dihydropyrazole ring nitrogen atoms;  $X^1$  is halogen, and  $X^2$  will contain at least one heteroatom.

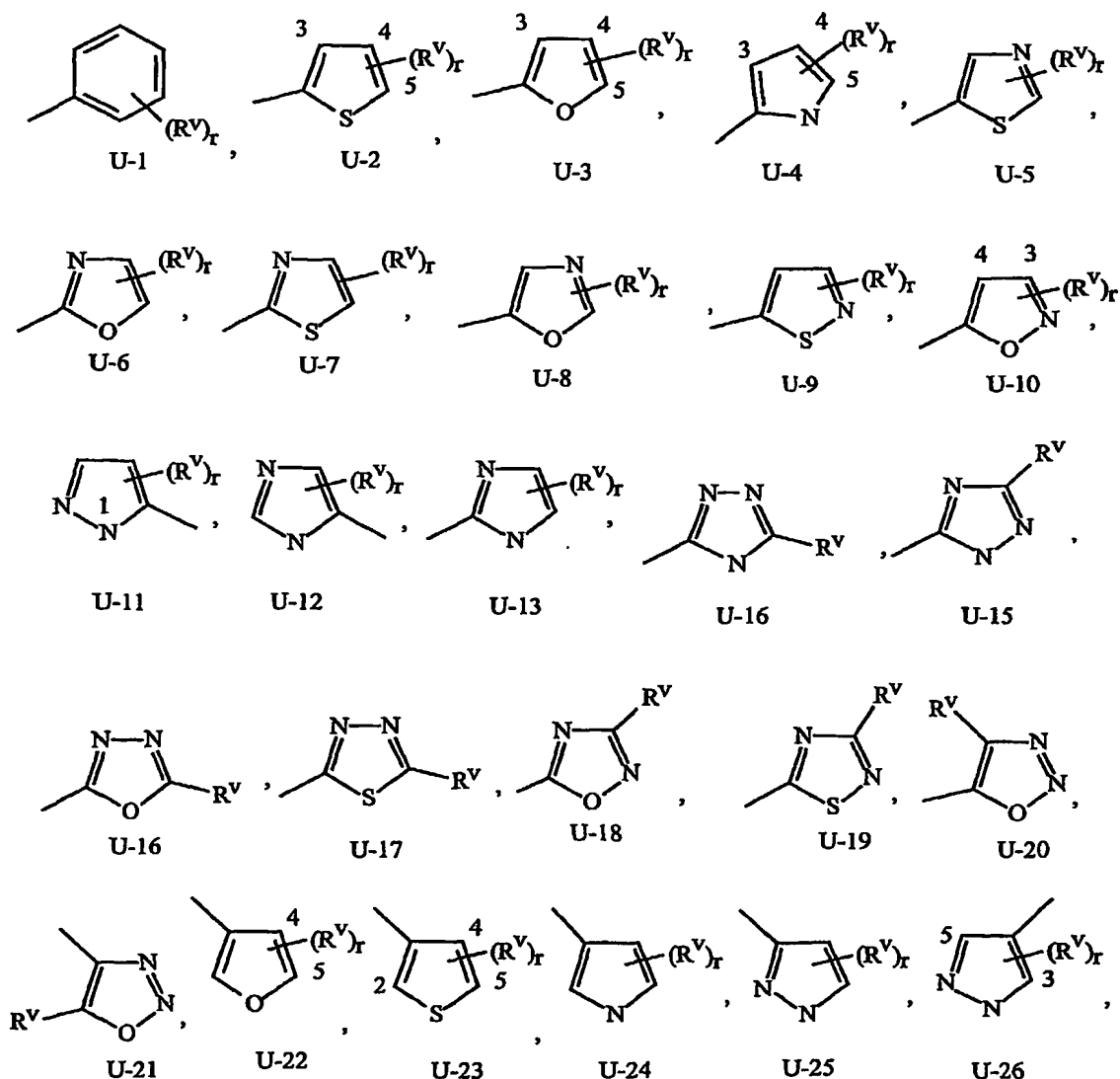
Although there is no definite limit to the size of L and R (including  $R^4$ ), optionally substituted alkyl moieties in L and R (including  $R^4$ ) commonly include 1 to 6 carbon atoms, more commonly 1 to 4 carbon atoms and most commonly 1 to 2 carbon atoms in the alkyl chain. Optionally substituted alkenyl and alkynyl moieties in L and R (including  $R^4$ ) commonly include 2 to 6 carbon atoms, more commonly 2 to 4 carbon atoms and most commonly 2 to 3 carbon atoms in the alkenyl or alkynyl chain.

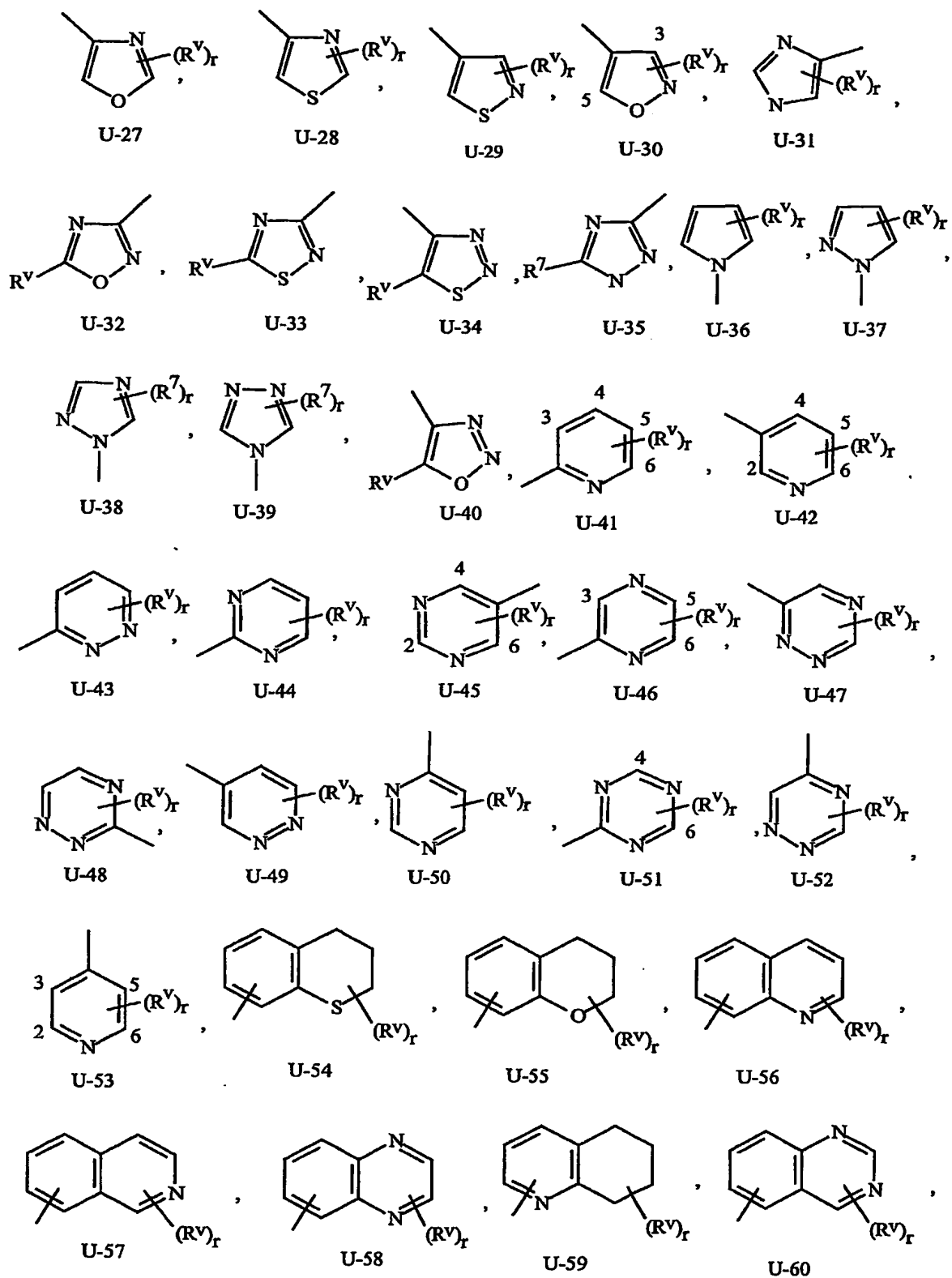
Also, there is no definite limit to the size of the groups listed for  $R^1$  and  $R^2$  but alkyl, including derivatives such as alkoxy and haloalkyl, is commonly  $C_1-C_6$ , more commonly  $C_1-C_4$ , and most commonly  $C_1-C_2$ .

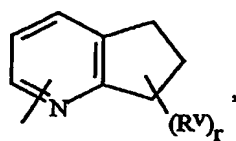
As indicated above, the carbon moieties L, R and  $R^4$  may be (among others) an aromatic ring or ring system. Examples of aromatic rings or ring systems include a phenyl ring, 5- or 6-membered heteroaromatic rings aromatic 8-, 9- or 10-membered fused carbobicyclic ring systems and aromatic 8-, 9- or 10-membered fused heterobicyclic ring systems wherein each ring or ring system is optionally substituted. The term "optionally substituted" in connection with these J groups refers to groups that are unsubstituted or have at least one non-hydrogen substituent. These carbon moieties may be substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, the number of optional substituents (when present) ranges from one to four. An example of phenyl optionally substituted with from one to four substituents is the ring illustrated as U-1 in Exhibit 1, wherein  $R^v$  is any non-hydrogen substituent and r is an integer from 0 to 4. Examples of aromatic 8-, 9- or 10-membered fused carbobicyclic ring systems optionally substituted with from one to four substituents include a naphthyl group optionally substituted with from one to four substituents illustrated as U-85 and a 1,2,3,4-tetrahydronaphthyl group optionally substituted with from one to four substituents illustrated as U-86 in Exhibit 1, wherein  $R^v$  is any substituent and r is an integer from 0 to 4. Examples of 5- or 6-membered heteroaromatic rings optionally substituted with from one to four substituents include the rings U-2 through U-53 illustrated in Exhibit 1 wherein  $R^v$  is any substituent and r is an integer from 1 to 4. Examples of aromatic 8-, 9- or 10-membered fused heterobicyclic ring systems optionally substituted with from one to four substituents include U-54 through U-84 illustrated in Exhibit 1 wherein  $R^v$  is any substituent and r is an integer from 0 to 4. Other examples of L and R include include a benzyl group optionally substituted with from one to four substituents illustrated as U-87 and a benzoyl group optionally substituted with from one to four substituents illustrated as U-88 in Exhibit 1, wherein  $R^v$  is any substituent and r is an integer from 0 to 4.

- Although  $R^V$  groups are shown in the structures U-1 through U-85, it is noted that they do not need to be present since they are optional substituents. The nitrogen atoms that require substitution to fill their valence are substituted with H or  $R^V$ . Note that some U groups can only be substituted with less than 4  $R^V$  groups (e.g. U-14, U-15, U-18 through U-21 and U-32 through U-34 can only be substituted with one  $R^V$ ). Note that when the attachment point between  $(R^V)_r$  and the U group is illustrated as floating,  $(R^V)_r$  can be attached to any available carbon atom or nitrogen atom of the U group. Note that when the attachment point on the U group is illustrated as floating, the U group can be attached to the remainder of Formulae I and II through any available carbon of the U group by replacement of a hydrogen atom.

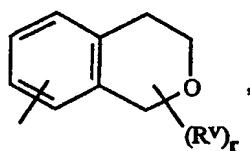
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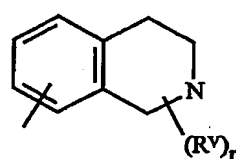




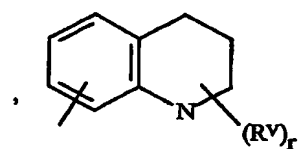
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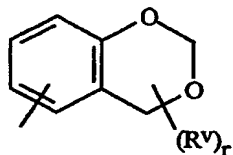
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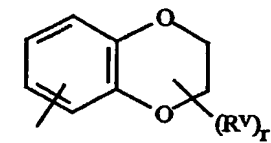
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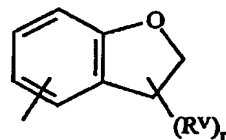
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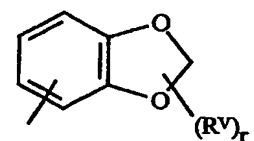
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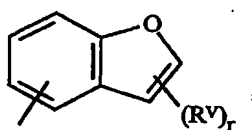
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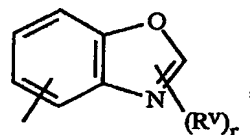
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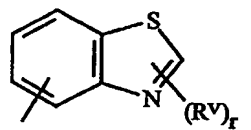
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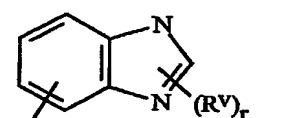
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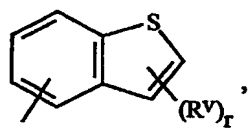
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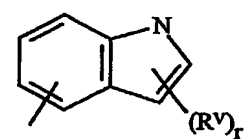
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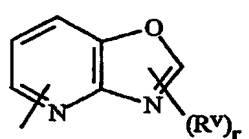
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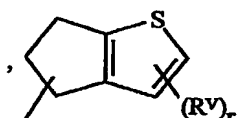
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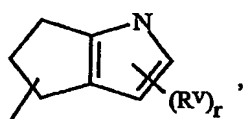
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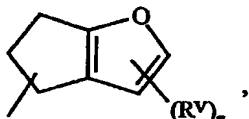
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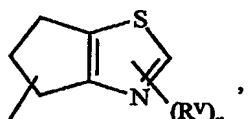
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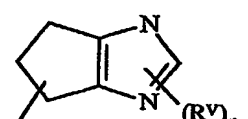
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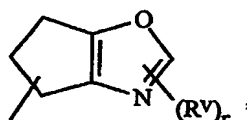
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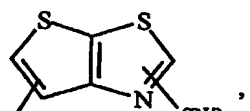
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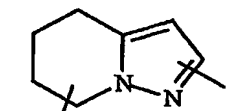
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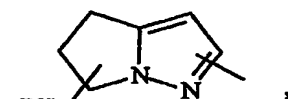
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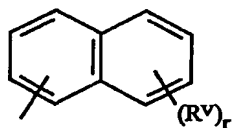
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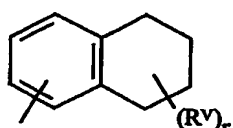
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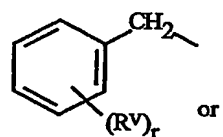
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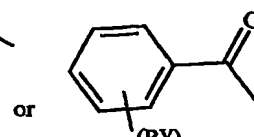
U-85



U-86



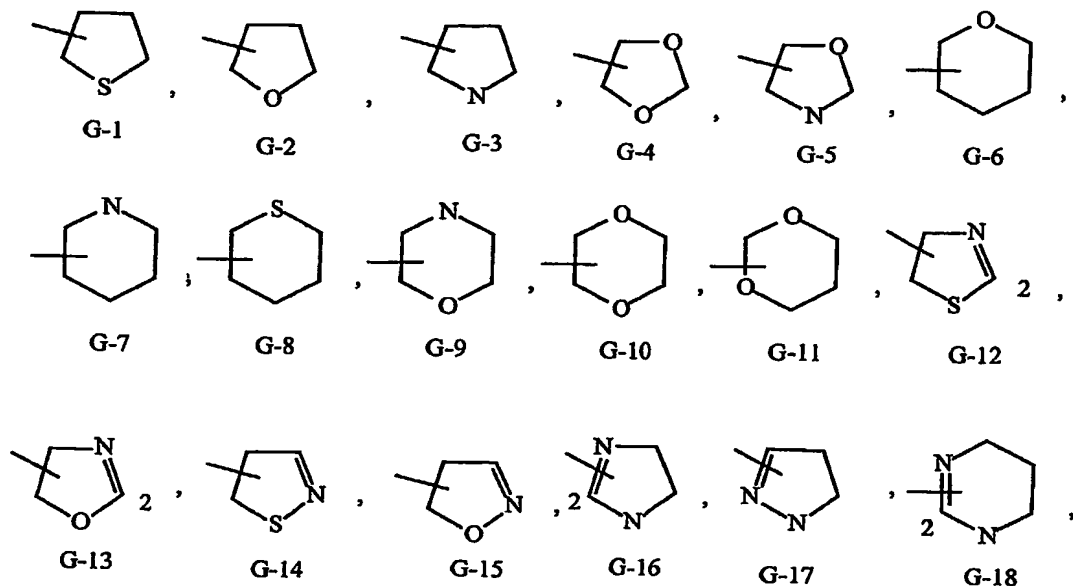
U-87

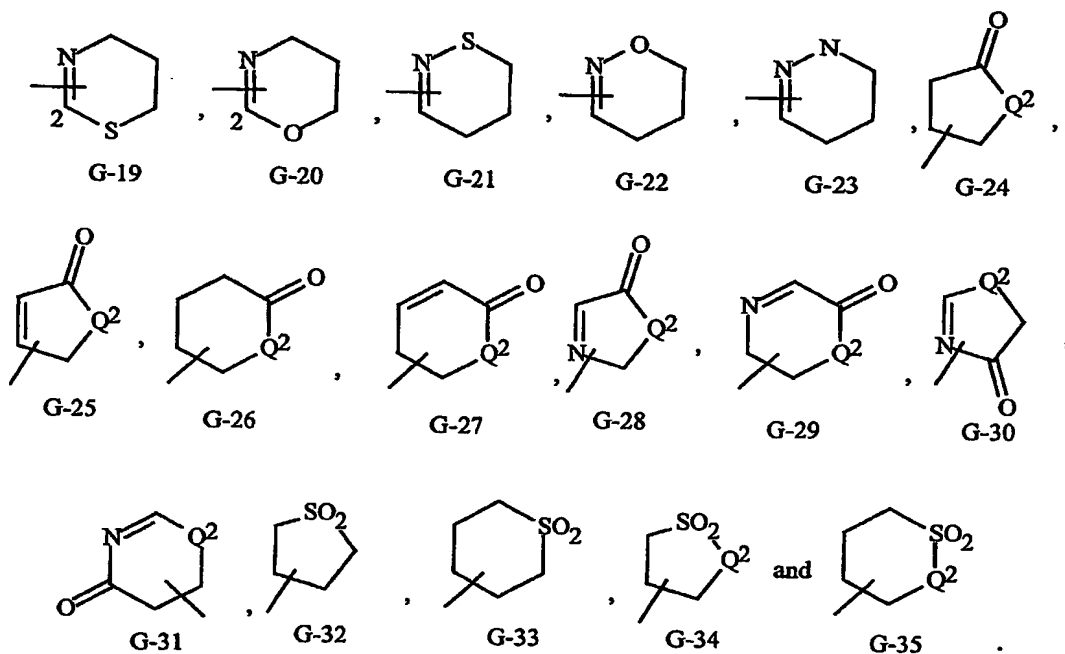


U-88

As indicated above, the carbon moieties L, R and R<sup>4</sup> may be (among others) saturated or partially saturated carbocyclic and heterocyclic rings, which can be further optionally substituted. The term "optionally substituted" in connection with these L and R carbon moieties refers to carbon moieties which are unsubstituted or have at least one non-hydrogen substituent. These carbon moieties may be substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, the number of optional substituents (when present) ranges from one to four. Examples of saturated or partially saturated carbocyclic rings include optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl and optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl. Examples of saturated or partially saturated heterocyclic rings include 5- or 6-membered nonaromatic heterocyclic rings optionally including one or two ring members selected from the group consisting of C(=O), SO or S(O)<sub>2</sub>, optionally substituted. Examples of such L and R carbon moieties include those illustrated as G-1 through G-35 in Exhibit 2. Note that when the attachment point on these G groups is illustrated as floating, the G group can be attached to the remainder of Formulae I and II through any available carbon or nitrogen of the G group by replacement of a hydrogen atom. The optional substituents can be attached to any available carbon or nitrogen by replacing a hydrogen atom (said substituents are not illustrated in Exhibit 2 since they are optional substituents). Note that when G comprises a ring selected from G-24 through G-31, G-34 and G-35, Q<sup>2</sup> may be selected from O, S, NH or substituted N.

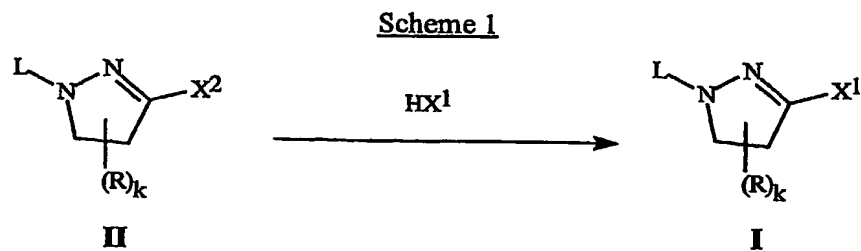
### Exhibit 2





It is noted that the L, R and R<sup>4</sup> carbon moieties may be optionally substituted. As noted above, L and R carbon moieties may commonly comprise, among other groups, a U group or a G group further optionally substituted with from one to four substituents. Thus the L and R carbon moieties may comprise a U group or a G group selected from U-1 through U-88 or G-1 through G-35, and further substituted with additional substituents including one to four U or G groups (which may be the same or different) with both the core U or G group and substituent U or G groups optionally further substituted. Of particular note are L carbon moieties comprising a U group optionally substituted with from one to three additional substituents. For example, L can be the group U-41.

As shown in Scheme 1, according to the method of this invention a 4,5-dihydro-1H-pyrazole of Formula II in contacted with HX<sup>1</sup> to form a different 3-halo-4,5-dihydro-1H-pyrazole compound of Formula I.



wherein L, R, X<sup>1</sup>, X<sup>2</sup> and k are as defined in the Summary of the Invention.

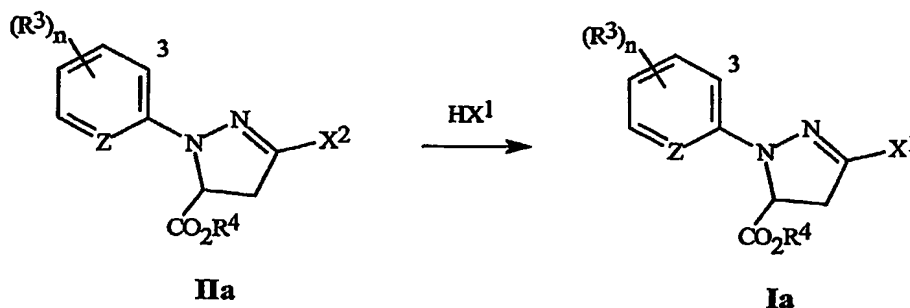
The reaction is conducted in a suitable solvent. For best results the solvent should be non-nucleophilic, relatively inert to HX<sup>1</sup> and capable of dissolving the compound of Formula II.

Suitable solvents include dibromomethane, dichloromethane and acetonitrile. The reaction can be conducted at or near atmospheric pressure or above atmospheric pressure in a pressure vessel. When  $X^2$  in the compound of Formula II is a halogen such as Cl, the reaction is preferably conducted in a way such that the  $HX^2$  generated by the reaction is removed by sparging or other suitable means. The reaction can be conducted between about 0 and 100 °C, most conveniently near ambient temperature (e.g., about 10–40 °C), and most preferably between about 20 and 30 °C. Addition of a Lewis acid catalyst (e.g., aluminum bromide for preparing Formula I wherein  $X^1$  is Br) can facilitate the reaction. The product of Formula I is isolated by the usual methods known to those skilled in the art, including extraction, distillation and crystallization.

For the method of this invention, preferred starting compounds include compounds of Formula II wherein  $m$  is 2 and  $p$  is 1. Also preferred are starting compounds of Formula II wherein  $X^2$  is halogen or  $OS(O)_mR^1$  (especially where  $m$  is 2). Further preferred are starting compounds of Formula II wherein  $X^2$  is Cl or  $OS(O)_mR^1$ ,  $m$  is 2, and  $R^1$  is  $C_1$ – $C_6$  alkyl,  $CF_3$  or phenyl optionally substituted with from 1 to 3 substituents selected from  $C_1$ – $C_4$  alkyl, and more preferably  $R^1$  is  $C_1$ – $C_2$  alkyl, phenyl or 4-methylphenyl. Particularly preferred methods of this invention include those using a starting compound of Formula II wherein  $X^2$  is Cl or  $OS(O)_2R^1$ , and  $R^1$  is methyl, phenyl or 4-methylphenyl. Especially preferred method of this invention include those using a starting compound of Formula II wherein  $X^2$  is Cl or  $OS(O)_2R^1$ , and  $R^1$  is phenyl or 4-methylphenyl.

Preferred methods of this invention include the method wherein the starting compound of Formula II is Formula IIa and the product compound of Formula I is Formula Ia as shown in Scheme 2 below.

Scheme 2



wherein  $X^1$  and  $X^2$  are as defined for Formulae I and II;

each  $R^3$  is independently  $C_1$ – $C_4$  alkyl,  $C_2$ – $C_4$  alkenyl,  $C_2$ – $C_4$  alkynyl,  $C_3$ – $C_6$  cycloalkyl,  $C_1$ – $C_4$  haloalkyl,  $C_2$ – $C_4$  haloalkenyl,  $C_2$ – $C_4$  haloalkynyl,  $C_3$ – $C_6$  halocycloalkyl, halogen, CN,  $NO_2$ ,  $C_1$ – $C_4$  alkoxy,  $C_1$ – $C_4$  haloalkoxy,  $C_1$ – $C_4$  alkylthio,  $C_1$ – $C_4$  alkylsulfinyl,  $C_1$ – $C_4$  alkylsulfonyl,  $C_1$ – $C_4$  alkylamino,  $C_2$ – $C_8$  dialkylamino,  $C_3$ – $C_6$  cycloalkylamino,  $(C_1$ – $C_4$  alkyl)( $C_3$ – $C_6$  cycloalkyl)amino,

$C_2-C_4$  alkylcarbonyl,  $C_2-C_6$  alkoxy carbonyl,  $C_2-C_6$  alkylaminocarbonyl,  
 $C_3-C_8$  dialkylaminocarbonyl or  $C_3-C_6$  trialkylsilyl;

$R^4$  is H or an optionally substituted carbon moiety;

Z is N or  $CR^5$ ;

5  $R^5$  is H or  $R^3$ ; and

n is an integer selected from 0 to 3.

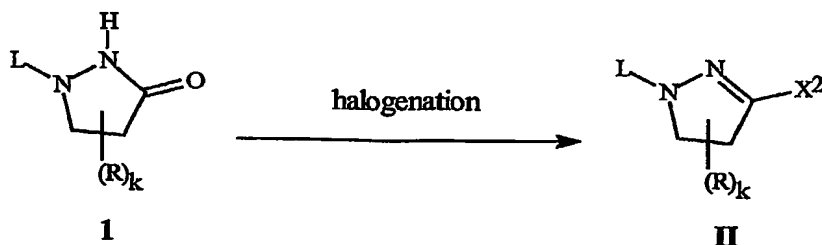
One skilled in the art will recognize that Formula Ia is a subgenus of Formula I, and Formula IIa is subgenus of Formula II.

10 While a wide range of optionally substituted carbon moieties as already described are useful as  $R^4$  in esters of Formula Ia for the method of Scheme 2, commonly  $R^4$  is a radical containing up to 18 carbon atoms and selected from alkyl, alkenyl and alkynyl; and benzyl and phenyl, each optionally substituted with alkyl and halogen. Most preferably  $R^4$  is  $C_1-C_4$  alkyl.

15 Of note is the method shown in Scheme 2 wherein Z is N, n is 1 and  $R^3$  is Cl or Br and is located at the 3-position. Also of note is the method shown in Scheme 2 wherein  $X^2$  is halogen or  $OS(O)_2R^1$ , particularly where  $R^1$  is methyl, phenyl or 4-methylphenyl. Also of note is the method shown in Scheme 2 wherein  $X^1$  is Br or Cl and more particularly  $X^1$  is Br. Of particular note is the method shown in Scheme 2 wherein  $X^1$  is Br,  $X^2$  is Cl or  $OS(O)_mR^1$ , m is 2, and  $R^1$  is phenyl or 4-methylphenyl.

20 Starting compounds of Formula II wherein  $X^2$  is halogen can be prepared from corresponding compounds of Formula 1 as shown in Scheme 3

Scheme 3



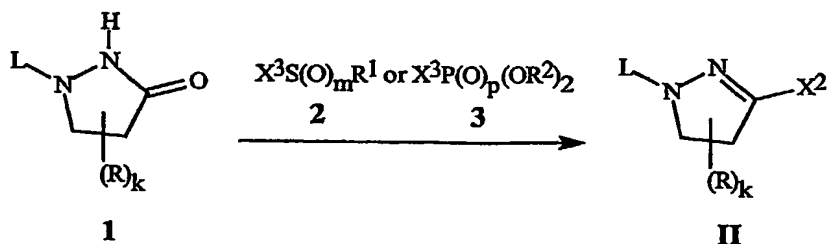
wherein  $X^2$  is halogen and L, R and k are as previously defined.

25 Treatment of a compound of Formula 1 with a halogenating reagent, usually in the presence of a solvent, affords the corresponding halo compound of Formula II. Halogenating reagents that can be used include phosphorus oxyhalides, phosphorus trihalides, phosphorus pentahalides, thionyl chloride, dihalotrialkylphosphoranes, dihalodiphenylphosphoranes, oxalyl chloride, phosgene, sulfur tetrafluoride and (diethylamino)sulfur trifluoride. Preferred  
 30 are phosphorus oxyhalides and phosphorus pentahalides. To obtain complete conversion, at least 0.33 equivalents of phosphorus oxyhalide versus the compound of Formula 1 (i.e. the mole ratio of phosphorus oxyhalide to Formula 1 is at least 0.33) should be used, preferably



As shown in Scheme 4, starting compounds of Formula II wherein  $R^1$  is a  $OS(O)_mR^1$  or  $OP(O)_p(OR^2)_2$  can likewise be prepared from corresponding compounds of Formula 1 by contacting with  $X^3S(O)_mR^1$  (2) or  $X^3P(O)_p(OR^2)_2$  (3), respectively, wherein  $X^3$  is a nucleophilic reaction leaving group. Halides such as Cl are particularly useful for  $X^3$ . Also useful for  $X^3S(O)_mR^1$  is  $X^3$  being  $OS(O)_mR^1$  (i.e. Formula 2 is  $R^1S(O)_mOS(O)_mR^1$ );  $X^3$  being  $OS(O)_mR^1$  is particularly useful when  $R^1$  is  $CF_3$ . In view of synthetic accessibility and relatively low cost,  $X^3$  being Cl is generally preferred.

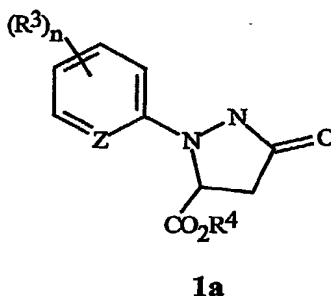
### Scheme 4



In this method, the compound of Formula 1 is contacted with a compound of Formula 2 (for X<sup>2</sup> being OS(O)<sub>m</sub>R<sup>1</sup>) or Formula 3 (for X<sup>2</sup> being OP(O)<sub>n</sub>(OR<sup>2</sup>)<sub>2</sub>), typically in the presence

of a solvent and a base. Suitable solvents include dichloromethane, tetrahydrofuran, acetonitrile and the like. Suitable bases include tertiary amines (e.g., triethylamine, *N,N*-diisopropylethylamine) and ionic bases such as potassium carbonate and the like. A tertiary amine is preferred as the base. At least one of equivalent (preferably a small excess, e.g., 5–10%) of the compound of Formula 2 or Formula 3 and the base relative to the compound Formula 1 is generally used to give complete conversion. The reaction is typically conducted at a temperature between about  $-50^{\circ}\text{C}$  and the boiling point of the solvent, more commonly between about  $0^{\circ}\text{C}$  and ambient temperature (i.e. about  $15$  to  $30^{\circ}\text{C}$ ). The reaction is typically complete within a couple hours to several days; the progress of the reaction can be monitored by such techniques known to those skilled in the art as thin layer chromatography and analysis of the  $^1\text{H}$  NMR spectrum. The reaction mixture is then worked up, such as by washing with water, drying the organic phase and evaporating the solvent. The desired product, a compound of Formula II, can be isolated by methods known to those skilled in the art, including extraction, crystallization and distillation.

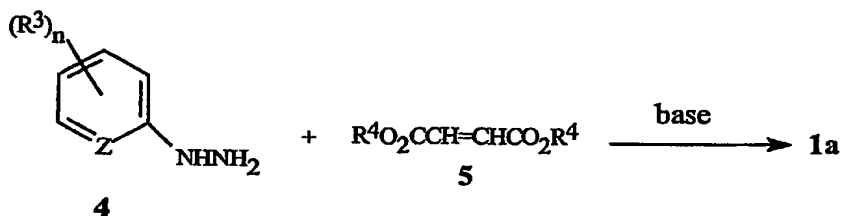
As Formula IIa is a subgenus of Formula II, compounds of Formula IIa can be prepared from corresponding compounds of Formula 1a, which is a subgenus of Formula 1, by the methods already described for Schemes 3 and 4.



wherein  $\text{R}^3$ ,  $\text{R}^4$ , Z and n are as defined for Formula IIa.

Compounds of Formula 1 can be prepared by the great variety of modern synthetic methodologies known to those skilled in the art. For example, compounds of Formula 1a can be prepared from compounds of Formulae 4 and 5 as outlined in Scheme 5.

Scheme 5



In this method, a hydrazine compound of Formula 4 is contacted with a compound of Formula 5 (a fumarate ester or maleate ester or a mixture thereof may be used) in the presence of a base and a solvent. The base is typically a metal alkoxide salt, such as sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, potassium *tert*-butoxide, lithium *tert*-butoxide, and the like. Greater than 0.5 equivalents of base versus the compound of Formula 4 should be used, preferably between 0.9 and 1.3 equivalents. Greater than 1.0 equivalents of the compound of Formula 5 should be used, preferably between 1.0 to 1.3 equivalents. Polar protic and polar aprotic organic solvents can be used, such as alcohols, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide, dimethyl sulfoxide and the like. Preferred solvents are alcohols such as methanol and ethanol. It is especially preferred that the alcohol be the same as that making up the fumarate or maleate ester and the alkoxide base. The reaction is typically conducted by mixing the compound of Formula 4 and the base in the solvent. The mixture can be heated or cooled to a desired temperature and the compound of Formula 5 added over a period of time. Typically reaction temperatures are between 0 °C and the boiling point of the solvent used. The reaction may be conducted under greater than atmospheric pressure in order to increase the boiling point of the solvent. Temperatures between about 30 and 90 °C are generally preferred. The addition time can be as quick as heat transfer allows. Typical addition times are between 1 minute and 2 hours. Optimum reaction temperature and addition time vary depending upon the identities of the compounds of Formula 4 and Formula 5. After addition, the reaction mixture can be held for a time at the reaction temperature. Depending upon the reaction temperature, the required hold time may be from 0 to 2 hours. Typical hold times are 10 to 60 minutes. The reaction mass then can be acidified by adding an organic acid, such as acetic acid and the like, or an inorganic acid, such as hydrochloric acid, sulfuric acid and the like. Depending on the reaction conditions and the means of isolation, the -CO<sub>2</sub>R<sup>4</sup> function on the compound of Formula 1a may be hydrolyzed to -CO<sub>2</sub>H; for example, the presence of water in the reaction mixture can promote such hydrolysis. If the carboxylic acid (-CO<sub>2</sub>H) is formed, it can be converted back to -CO<sub>2</sub>R<sup>4</sup> wherein R<sup>4</sup> is, for example, C<sub>1</sub>-C<sub>4</sub> alkyl using esterification methods well-known in the art. The desired product, a compound of Formula 1a, can be isolated by methods known to those skilled in the art, such as crystallization, extraction or distillation.

It is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Steps in the following Examples illustrate a procedure for each step in an overall synthetic transformation, and the starting material for each step may not have necessarily been prepared by a particular preparative run whose procedure is described in other Examples or Steps. Percentages are by weight except for chromatographic solvent mixtures or where

otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated.  $^1\text{H}$  NMR spectra are reported in ppm downfield from tetramethylsilane; "s" means singlet, "d" means doublet, "t" means triplet, "q" means quartet, "m" means multiplet, "dd" means doublet of doublets, "dt" means doublet of triplets, and "br s" means broad singlet.

## EXAMPLE 1

Preparation of ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate by replacement of chlorine with bromine

Step A: Preparation of ethyl 2-(3-chloro-2-pyridinyl)-5-oxo-3-pyrazolidine-carboxylate

A 2-L four-necked flask equipped with a mechanical stirrer, thermometer, addition funnel, reflux condenser, and nitrogen inlet was charged with absolute ethanol (250 mL) and an ethanolic solution of sodium ethoxide (21%, 190 mL, 0.504 mol). The mixture was heated to reflux at about 83 °C. It was then treated with 3-chloro-2(1*H*)-pyridinone hydrazone (68.0 g, 0.474 mol). The mixture was re-heated to reflux over a period of 5 minutes. The yellow slurry was then treated dropwise with diethyl maleate (88.0 mL, 0.544 mol) over a period of 5 minutes. The reflux rate increased markedly during the addition. By the end of the addition all of the starting material had dissolved. The resulting orange-red solution was held at reflux for 10 minutes. After being cooled to 65 °C, the reaction mixture was treated with glacial acetic acid (50.0 mL, 0.873 mol). A precipitate formed. The mixture was diluted with water (650 mL), causing the precipitate to dissolve. The orange solution was cooled in an ice bath. Product began to precipitate at 28 °C. The slurry was held at about 2 °C for 2 hours. The product was isolated via filtration, washed with aqueous ethanol (40%, 3 x 50 mL), and then air-dried on the filter for about 1 hour. The title product compound was obtained as a highly crystalline, light orange powder (70.3 g, 55% yield). No significant impurities were observed by  $^1\text{H}$  NMR.

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.22 (t, 3H), 2.35 (d, 1H), 2.91 (dd, 1H), 4.20 (q, 2H), 4.84 (d, 1H), 7.20 (dd, 1H), 7.92 (d, 1H), 8.27 (d, 1H), 10.18 (s, 1H).

Step B: Preparation of ethyl 3-chloro-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate

To a 2-L four-necked flask equipped with a mechanical stirrer, thermometer, reflux condenser, and nitrogen inlet was charged acetonitrile (1000 mL), ethyl 2-(3-chloro-2-pyridinyl)-5-oxo-3-pyrazolidinecarboxylate (i.e. the product of Step A) (91.0 g, 0.337 mol) and phosphorus oxychloride (35.0 mL, 0.375 mol). Upon adding the phosphorus oxychloride, the mixture self-heated from 22 to 25 °C and a precipitate formed. The light-yellow slurry was heated to reflux at 83 °C over a period of 35 minutes, whereupon the precipitate dissolved. The resulting orange solution was held at reflux for 45 minutes,

whereupon it had become black-green. The reflux condenser was replaced with a distillation head, and 650 mL of solvent was removed by distillation. A second 2-L four-necked flask equipped with a mechanical stirrer was charged with sodium bicarbonate (130 g, 1.55 mol) and water (400 mL). The concentrated reaction mixture was added to the sodium bicarbonate slurry over a period of 15 minutes. The resulting, two-phase mixture was stirred vigorously for 20 minutes, at which time gas evolution had ceased. The mixture was diluted with dichloromethane (250 mL) and then was stirred for 50 minutes. The mixture was treated with Celite® 545 diatomaceous earth filter aid (11 g) and then filtered to remove a black, tarry substance that inhibited phase separation. Since the filtrate was slow to separate into distinct phases, it was diluted with dichloromethane (200 mL) and water (200 mL) and treated with more Celite® 545 (15 g). The mixture was filtered, and the filtrate was transferred to a separatory funnel. The heavier, deep green organic layer was separated. A rag layer (50 mL) was refiltered and then added to the organic layer. The organic solution (800 mL) was treated with magnesium sulfate (30 g) and silica gel (12 g), and the slurry was stirred magnetically for 30 minutes. The slurry was filtered to remove the magnesium sulfate and silica gel, which had become deep blue-green. The filter cake was washed with dichloromethane (100 mL). The filtrate was concentrated on a rotary evaporator. The product consisted of dark amber oil (92.0 g, 93% yield). The only appreciable impurities observed by  $^1\text{H}$  NMR were 1% starting material and 0.7% acetonitrile.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.15 (t, 3H), 3.26 (dd, 1H), 3.58 (dd, 1H), 4.11 (q, 2H), 5.25 (dd, 1H), 7.00 (dd, 1H), 7.84 (d, 1H), 8.12 (d, 1H).

Step C: Preparation of ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate

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Hydrogen bromide was passed through a solution of ethyl 3-chloro-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (i.e. product of Step B) (8.45 g, 29.3 mmol) in dibromomethane (85 mL). After 90 minutes the gas flow was terminated, and the reaction mixture was washed with aqueous sodium bicarbonate solution (100 mL). The organic phase was dried and evaporated under reduced pressure to give the title product as an oil (9.7 g, 99% yield), which crystallized on standing.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.19 (t, 3H), 3.24 (1/2 of AB in ABX pattern,  $J = 9.3, 17.3$  Hz, 1H), 3.44 (1/2 of AB in ABX pattern,  $J = 11.7, 17.3$  Hz, 1H), 4.18 (q, 2H), 5.25 (X of ABX, 1H,  $J = 9.3, 11.9$  Hz), 6.85 (dd,  $J = 4.7, 7.7$  Hz, 1H), 7.65 (dd,  $J = 1.6, 7.8$  Hz, 1H), 8.07 (dd,  $J = 1.6, 4.8$  Hz, 1H).

## EXAMPLE 2

Preparation of ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate by replacement of tosylate with bromine

Step A: Preparation of ethyl 1-(3-chloro-2-pyridinyl)-4,5-dihydro-3-[[4-methylphenyl)sulfonyl]oxy]-1*H*-pyrazole-5-carboxylate

Triethylamine (3.75 g, 37.1 mmol) was added dropwise to a mixture of ethyl 2-(3-chloro-2-pyridinyl)-5-oxo-3-pyrazolidinecarboxylate (i.e. the product of Example 1, Step A) (10.0 g, 37.1 mmol) and *p*-toluenesulfonyl chloride (7.07 g, 37.1 mmol) in dichloromethane (100 mL) at 0 °C. Further portions of *p*-toluenesulfonyl chloride (0.35 g, 1.83 mmol) and triethylamine (0.19 g, 1.88 mmol) were added. The reaction mixture was then allowed to warm to room temperature and was stirred overnight. The mixture was then diluted with dichloromethane (200 mL) and washed with water (3 x 70 mL). The organic phase was dried and evaporated to leave the title product as an oil (13.7 g, 87% yield), which slowly formed crystals. Product recrystallized from ethyl acetate/hexanes melted at 99.5–100 °C.

IR (nujol): 1740, 1638, 1576, 1446, 1343, 1296, 1228, 1191, 1178, 1084, 1027, 948, 969, 868, 845 cm<sup>-1</sup>.

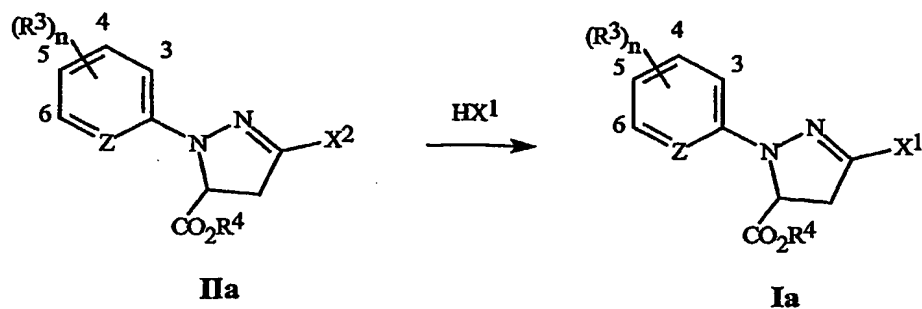
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.19 (t, 3H), 2.45 (s, 3H), 3.12 (1/2 of AB in ABX pattern, *J* = 17.3, 9 Hz, 1H), 3.33 (1/2 of AB in ABX pattern, *J* = 17.5, 11.8 Hz, 1H), 4.16 (q, 2H), 5.72 (X of ABX, *J* = 9, 11.8 Hz, 1H), 6.79 (dd, *J* = 4.6, 7.7 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.56 (dd, *J* = 1.6, 7.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 8.01 (dd, *J* = 1.4, 4.6 Hz, 1H).

Step B: Preparation of ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate

Hydrogen bromide was passed through a solution of ethyl 1-(3-chloro-2-pyridinyl)-4,5-dihydro-3-[[4-methylphenyl)sulfonyl]oxy]-1*H*-pyrazole-5-carboxylate (i.e. product of Step A) (5 g, 11.8 mmol) in dibromomethane (50 mL). After about 60 minutes the gas flow was terminated, and the reaction mixture was washed with aqueous sodium bicarbonate solution (50 mL). The organic phase was dried and evaporated under reduced pressure to give the title product as an oil (3.92 g, 100% yield), which crystallized on standing. The <sup>1</sup>H NMR spectrum of the product was the same as reported for the product of Example 1, Step C.

By the procedures described herein together with methods known in the art, the compounds of Formula I can be converted to compounds of Formula II as illustrated for Formulae Ia and IIa in Table 1. The following abbreviations are used in the Table: *t* is tertiary, *s* is secondary, *n* is normal, *i* is iso, Me is methyl, Et is ethyl, Pr is propyl, *i*-Pr is isopropyl, *t*-Bu is tertiary butyl and Ph is phenyl.

TABLE I

X<sup>1</sup> is Br; X<sup>2</sup> is OS(O)<sub>2</sub>Ph

Z is N				Z is CH				Z is CCl				Z is CBr			
<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>
3-Cl	H	3-Br	H	3-Cl	H	3-Br	H	3-Cl	H	3-Br	H	3-Cl	H	3-Br	H
3-Cl	Me	3-Br	Me	3-Cl	Me	3-Br	Me	3-Cl	Me	3-Br	Me	3-Cl	Me	3-Br	Me
3-Cl	Et	3-Br	Et	3-Cl	Et	3-Br	Et	3-Cl	Et	3-Br	Et	3-Cl	Et	3-Br	Et
3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr	3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr	3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr	3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr
3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr	3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr	3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr	3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr
3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu	3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu	3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu	3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu
3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu	3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu	3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu	3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu
3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu	3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu	3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu	3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu
3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu	3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu	3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu	3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu

X<sup>1</sup> is Br; X<sup>2</sup> is OS(O)<sub>2</sub>Ph-4-Me

Z is N				Z is CH				Z is CCl				Z is CBr			
<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>
3-Cl	H	3-Br	H	3-Cl	H	3-Br	H	3-Cl	H	3-Br	H	3-Cl	H	3-Br	H
3-Cl	Me	3-Br	Me	3-Cl	Me	3-Br	Me	3-Cl	Me	3-Br	Me	3-Cl	Me	3-Br	Me
3-Cl	Et	3-Br	Et	3-Cl	Et	3-Br	Et	3-Cl	Et	3-Br	Et	3-Cl	Et	3-Br	Et
3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr	3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr	3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr	3-Cl	<i>n</i> -Pr	3-Br	<i>n</i> -Pr
3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr	3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr	3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr	3-Cl	<i>i</i> -Pr	3-Br	<i>i</i> -Pr
3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu	3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu	3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu	3-Cl	<i>n</i> -Bu	3-Br	<i>n</i> -Bu
3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu	3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu	3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu	3-Cl	<i>i</i> -Bu	3-Br	<i>i</i> -Bu
3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu	3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu	3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu	3-Cl	<i>s</i> -Bu	3-Br	<i>s</i> -Bu
3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu	3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu	3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu	3-Cl	<i>t</i> -Bu	3-Br	<i>t</i> -Bu

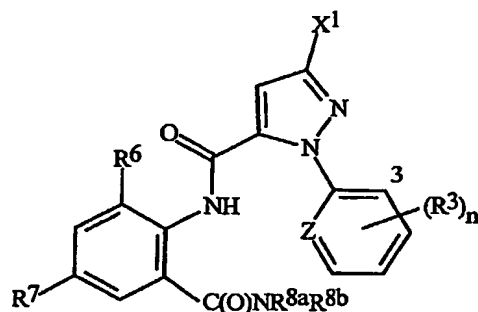




X <sup>1</sup> is Br; X <sup>2</sup> is OS(O) <sub>2</sub> Me											
<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>Z</u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>Z</u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>Z</u>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>Z</u>
3-Me	H	N	4-Me	H	CH	3-Br	H	N	3-CF <sub>3</sub>	H	N
5-Cl	Me	CH	3-OEt	Me	N	4-I	Me	CH	5-CF <sub>2</sub> H	Me	CH
4- <i>n</i> -Bu	Et	N	2-OCF <sub>3</sub>	Et	N	3-CN	Et	CH	6-CH <sub>3</sub>	Et	N
5-NMe <sub>2</sub>	<i>n</i> -Pr	CH	3-cyclo-Pr	<i>n</i> -Pr	CH	3-NO <sub>2</sub>	<i>n</i> -Pr	CH	3-CH <sub>2</sub> CF <sub>3</sub>	<i>n</i> -Pr	CH
3-OCH <sub>2</sub> F	<i>i</i> -Pr	N	H	<i>i</i> -Pr	N	3-S(O) <sub>2</sub> CH <sub>3</sub>	<i>i</i> -Pr	CH	6-cyclohexyl	<i>i</i> -Pr	CH
4-OCH <sub>3</sub>	<i>n</i> -Bu	CH	4-F	<i>n</i> -Bu	CCl	4-SCH <sub>3</sub>	<i>n</i> -Bu	CH	4-CH <sub>2</sub> CH=CH <sub>2</sub>	<i>n</i> -Bu	CH

X <sup>1</sup> is Br							
<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>Z</u>	X <sup>2</sup>	<u>R<sup>3</sup></u>	<u>R<sup>4</sup></u>	<u>Z</u>	X <sup>2</sup>
3-Cl	H	N	OS(O) <sub>2</sub> Et	3-Cl	H	N	OS(O) <sub>2</sub> CF <sub>3</sub>
3-Br	Me	CH	OS(O)Me	3-Br	Me	CH	OS(O) <sub>2</sub> - <i>n</i> -Bu
3-Cl	Et	N	OP(O)(OMe) <sub>2</sub>	3-Cl	Et	N	OP(O)(O- <i>i</i> -Pr) <sub>2</sub>
3-Br	<i>n</i> -Pr	CH	OP(OMe) <sub>2</sub>	3-Br	<i>n</i> -Pr	CH	OS(O) <sub>2</sub> Ph-2,4,6-tri-Me
3-Cl	<i>i</i> -Pr	N	OP(O)(OEt) <sub>2</sub>	3-Cl	<i>i</i> -Pr	N	OP(O)(OPh-4-Me) <sub>2</sub>
3-Br	<i>n</i> -Bu	CH	OP(O)(OPh) <sub>2</sub>	3-Br	<i>n</i> -Bu	CH	OS(O) <sub>2</sub> Ph-4-Cl

5 The 3-halo-4,5-dihydro-1*H*-pyrazole preparation method of the invention can be used to prepare a wide variety of compounds of Formula I that are useful as intermediates for the preparation of crop protection agents, pharmaceuticals and other fine chemicals. For example, compounds of Formula Ia are useful for preparing compounds of Formula III



III

10 wherein Z, X<sup>1</sup>, R<sup>3</sup> and n are defined as above; R<sup>6</sup> is CH<sub>3</sub>, F, Cl or Br; R<sup>7</sup> is F, Cl, Br, I or CF<sub>3</sub>; R<sup>8a</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl; and R<sup>8b</sup> is H or CH<sub>3</sub>. Preferably Z is N, n is 1, and R<sup>3</sup> is Cl or Br and is at the 3-position.

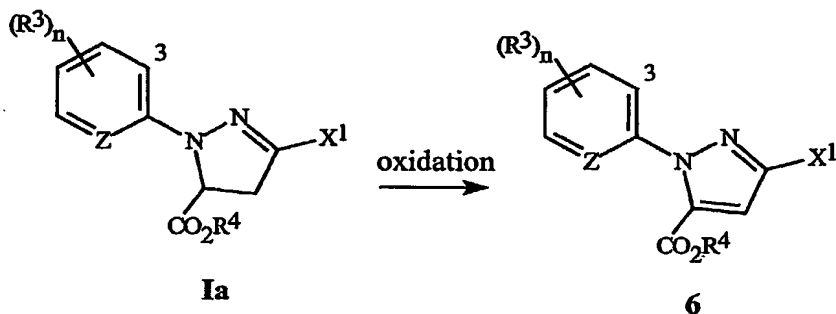
Compounds of Formula III are useful as insecticides, as described, for example, in PCT Publication No. WO 01/70671, published September 27, 2001, as well as in U.S. Patent

Application 60/324,173, filed September 21, 2001, U.S. Patent Application 60/323,941, filed September 21, 2001 and U.S. Patent Application 60/369,661, filed April 2, 2002. The preparation of compounds of Formula 8 and Formula III is described in U.S. Patent Application [BA9308 US PRV], filed concurrently herewith and hereby incorporated herein in its entirety by reference, as well as in U.S. Patent Application 60/369,660, filed April 2, 2002.

Compounds of Formula III can be prepared from corresponding compounds of Formula Ia by the processes outlined in Schemes 6-9.

As illustrated in Scheme 6, a compound of Formula Ia is treated with an oxidizing agent optionally in the presence of acid.

Scheme 6



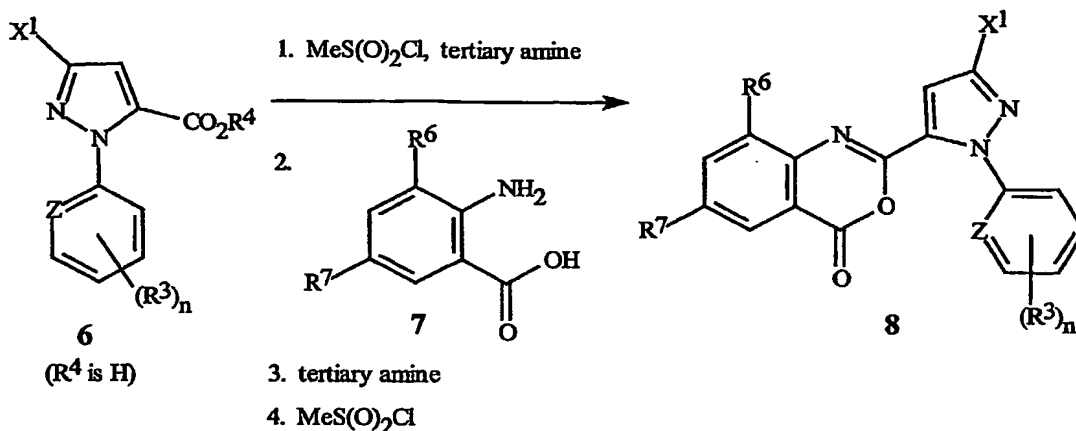
wherein  $R^3$ ,  $R^4$ ,  $Z$ ,  $X^1$  and  $n$  are as previously defined for Formula Ia.

A compound of Formula Ia wherein  $R^4$  is  $C_1$ - $C_4$  alkyl is preferred as starting material for this step. The oxidizing agent can be hydrogen peroxide, organic peroxides, potassium persulfate, sodium persulfate, ammonium persulfate, potassium monopersulfate (e.g., Oxone®) or potassium permanganate. To obtain complete conversion, at least one equivalent of oxidizing agent versus the compound of Formula Ia should be used, preferably from about one to two equivalents. This oxidation is typically carried out in the presence of a solvent. The solvent can be an ether, such as tetrahydrofuran, *p*-dioxane and the like, an organic ester, such as ethyl acetate, dimethyl carbonate and the like, or a polar aprotic organic such as *N,N*-dimethylformamide, acetonitrile and the like. Acids suitable for use in the oxidation step include inorganic acids, such as sulfuric acid, phosphoric acid and the like, and organic acids, such as acetic acid, benzoic acid and the like. The acid, when used, should be used in greater than 0.1 equivalents versus the compound of Formula Ia. To obtain complete conversion, one to five equivalents of acid can be used. For the compounds of Formula Ia wherein  $Z$  is  $CR^5$ , the preferred oxidant is hydrogen peroxide and the oxidation is preferably carried out in the absence of acid. For the compounds of Formula Ia wherein  $X$  is N, the preferred oxidant is potassium persulfate and the oxidation is preferably carried out in the presence of sulfuric acid. The reaction can be carried out by mixing the

compound of Formula 1a in the desired solvent and, if used, the acid. The oxidant can then be added at a convenient rate. The reaction temperature is typically varied from as low as about 0 °C up to the boiling point of the solvent in order to obtain a reasonable reaction time to complete the reaction, preferably less than 8 hours. The desired product, a compound of Formula 6 can be isolated by methods known to those skilled in the art, including extraction, chromatography, crystallization and distillation.

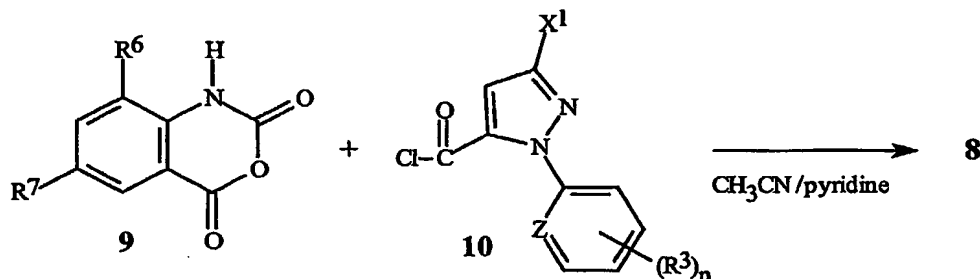
Carboxylic acid compounds of Formula 6 wherein  $R^4$  is H can be prepared by hydrolysis from corresponding ester compounds of Formula 6 wherein, for example,  $R^4$  is  $C_1$ - $C_4$  alkyl. Carboxylic ester compounds can be converted to carboxylic acid compounds by numerous methods including nucleophilic cleavage under anhydrous conditions or hydrolytic methods involving the use of either acids or bases (see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, Inc., New York, 1991, pp. 224-269 for a review of methods). For compounds of Formula 6, base-catalyzed hydrolytic methods are preferred. Suitable bases include alkali metal (such as lithium, sodium or potassium) hydroxides. For example, the ester can be dissolved in a mixture of water and an alcohol such as ethanol. Upon treatment with sodium hydroxide or potassium hydroxide, the ester is saponified to provide the sodium or potassium salt of the carboxylic acid. Acidification with a strong acid, such as hydrochloric acid or sulfuric acid, yields the carboxylic acid of Formula 6 wherein  $R^4$  is H. The carboxylic acid can be isolated by methods known to those skilled in the art, including extraction, distillation and crystallization.

Coupling of a pyrazolecarboxylic acid of Formula 6 wherein  $R^4$  is H with an anthranilic acid of Formula 7 provides the benzoxazinone of Formula 8. In Scheme 7, a benzoxazinone of Formula 8 is prepared directly via sequential addition of methanesulfonyl chloride in the presence of a tertiary amine such as triethylamine or pyridine to a pyrazolecarboxylic acid of Formula 6 wherein  $R^4$  is H, followed by the addition of an anthranilic acid of Formula 7, followed by a second addition of tertiary amine and methanesulfonyl chloride.

Scheme 7

This procedure generally affords good yields of the benzoxazinone.

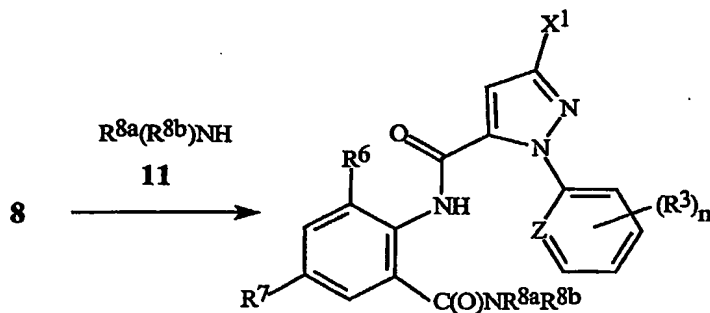
- 5 Scheme 8 depicts an alternate preparation for benzoxazinones of Formula 8 involving coupling of a pyrazole acid chloride of Formula 10 with an isatoic anhydride of Formula 9 to provide the Formula 8 benzoxazinone directly.

Scheme 8

- 10 Solvents such as pyridine or pyridine/acetonitrile are suitable for this reaction. The acid chlorides of Formula 10 are available from the corresponding acids of Formula 6 wherein  $\text{R}^4$  is H by known procedures such as chlorination with thionyl chloride or oxalyl chloride.

Compounds of Formula III can be prepared by the reaction of benzoxazinones of Formula 8 with  $\text{C}_1\text{--C}_4$  alkylamines and  $(\text{C}_1\text{--C}_4 \text{ alkyl})(\text{methyl})\text{amines}$  of Formula 11 as outlined in Scheme 9.

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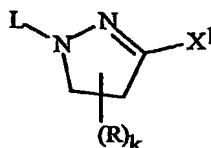
Scheme 9**III**

The reaction can be run neat or in a variety of suitable solvents including tetrahydrofuran, diethyl ether, dichloromethane or chloroform with optimum temperatures ranging from room temperature to the reflux temperature of the solvent. The general reaction of benzoxazinones with amines to produce anthranilamides is well documented in the chemical literature. For a review of benzoxazinone chemistry see Jakobsen et al., *Biorganic and Medicinal Chemistry* 2000, 8, 2095–2103 and references cited within. See also Coppola, *J. Heterocyclic Chemistry* 1999, 36, 563–588.

CLAIMS

What is claimed is:

1. A method for preparing a 3-halo-4,5-dihydro-1*H*-pyrazole compound of Formula I



I

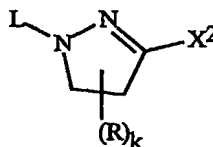
wherein L is an optionally substituted carbon moiety;

each R is independently selected from optionally substituted carbon moieties;

k is an integer from 0 to 4;

and X<sup>1</sup> is halogen; comprising:

- 10 contacting a 4,5-dihydro-1*H*-pyrazole compound of Formula II



II

wherein X<sup>2</sup> is OS(O)<sub>m</sub>R<sup>1</sup>, OP(O)<sub>p</sub>(OR<sup>2</sup>)<sub>2</sub> or a halogen other than X<sup>1</sup>;

m is 1 or 2;

p is 0 or 1;

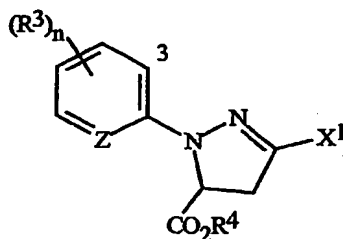
- 15 R<sup>1</sup> is selected from alkyl and haloalkyl; and phenyl optionally substituted with from 1 to 3 substituents selected from alkyl and halogen; and

each R<sup>2</sup> is independently selected from alkyl and haloalkyl; and phenyl optionally substituted with from 1 to 3 substituents selected from alkyl and halogen;

with a compound of the formula HX<sup>1</sup> in the presence of a suitable solvent.

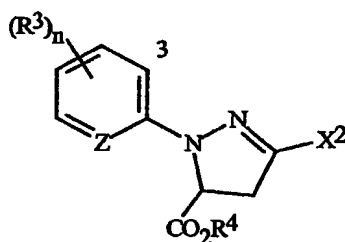
- 20 2. The method of Claim 1 wherein m is 2 and p is 1.
3. The method of Claim 2 wherein X<sup>2</sup> is halogen or OS(O)<sub>m</sub>R<sup>1</sup>.
4. The method of Claim 3 wherein X<sup>2</sup> is Cl or OS(O)<sub>m</sub>R<sup>1</sup> and R<sup>1</sup> is C<sub>1</sub>-C<sub>2</sub> alkyl, phenyl or 4-methylphenyl.

5. The method of Claim 1 wherein the compound of Formula I is of Formula Ia



Ia

and the compound of Formula II is of Formula IIa



IIa

5 wherein

each R<sup>3</sup> is independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>4</sub> haloalkenyl, C<sub>2</sub>-C<sub>4</sub> haloalkynyl, C<sub>3</sub>-C<sub>6</sub> halocycloalkyl, halogen, CN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>4</sub> alkylamino, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>3</sub>-C<sub>6</sub> cycloalkylamino, (C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub> cycloalkyl)amino, C<sub>2</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>6</sub> alkoxy carbonyl, C<sub>2</sub>-C<sub>6</sub> alkylaminocarbonyl, C<sub>3</sub>-C<sub>8</sub> dialkylaminocarbonyl or C<sub>3</sub>-C<sub>6</sub> trialkylsilyl;

R<sup>4</sup> is H or an optionally substituted carbon moiety;

Z is N or CR<sup>5</sup>;

15 R<sup>5</sup> is H or R<sup>3</sup>; and

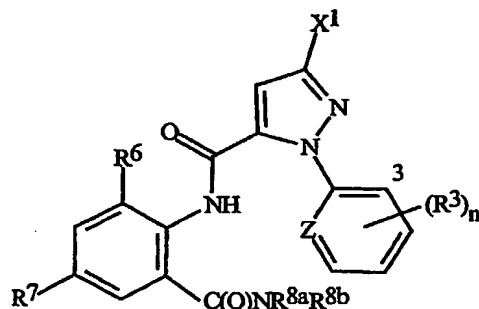
n is an integer from 0 to 3.

6. The method of Claim 5 wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl.

7. The method of Claim 6 wherein Z is N, n is 1, and R<sup>3</sup> is Cl or Br and is at the 3-position.

20 8. The method of Claim 6 wherein X<sup>1</sup> is Br, X<sup>2</sup> is Cl or OS(O)<sub>m</sub>R<sup>1</sup>, m is 2, and R<sup>1</sup> is phenyl or 4-methylphenyl.

## 9. A method of preparing a compound of Formula III



III

wherein

 $X^1$  is halogen;

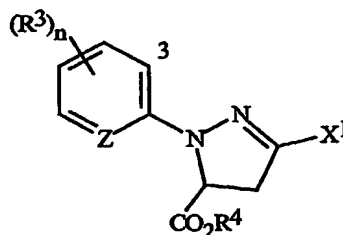
- 5 each  $R^3$  is independently  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_4$  alkenyl,  $C_2$ - $C_4$  alkynyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_4$  haloalkyl,  $C_2$ - $C_4$  haloalkenyl,  $C_2$ - $C_4$  haloalkynyl,  $C_3$ - $C_6$  halocycloalkyl, halogen, CN,  $NO_2$ ,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  haloalkoxy,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkylsulfinyl,  $C_1$ - $C_4$  alkylsulfonyl,  $C_1$ - $C_4$  alkylamino,  $C_2$ - $C_8$  dialkylamino,  $C_3$ - $C_6$  cycloalkylamino,  $(C_1$ - $C_4$  alkyl)( $C_3$ - $C_6$  cycloalkyl)amino,  $C_2$ - $C_4$  alkylcarbonyl,  $C_2$ - $C_6$  alkoxy carbonyl,  $C_2$ - $C_6$  alkylaminocarbonyl,  $C_3$ - $C_8$  dialkylaminocarbonyl or  $C_3$ - $C_6$  trialkylsilyl;

 $Z$  is N or  $CR^5$ ; $R^5$  is H or  $R^3$ ; $R^6$  is  $CH_3$ , F, Cl or Br;

- 15  $R^7$  is F, Cl, Br, I or  $CF_3$ ;

 $R^{8a}$  is  $C_1$ - $C_4$  alkyl; $R^{8b}$  is H or  $CH_3$ ; and $n$  is an integer from 0 to 3

using a compound of Formula Ia



Ia

20 wherein  $R^4$  is H or an optionally substituted carbon moiety, characterized by:  
preparing said compound of Formula Ia by the method of Claim 5.



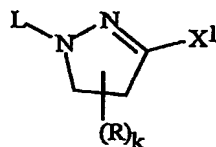
10. The method of Claim 9 wherein  $R^4$  is  $C_1-C_4$  alkyl.
11. The method of Claim 10 wherein Z is N, n is 1, and  $R^3$  is Cl or Br and is at the 3-position.
12. The method of Claim 10 wherein  $X^1$  is Br,  $X^2$  is Cl or  $OS(O)_mR^1$ , m is 2, and  $R^1$  is phenyl or 4-methylphenyl.

TITLE

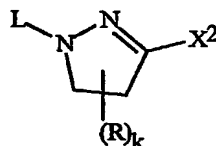
## METHOD FOR PREPARING 3-HALO-4,5-DIHYDRO-1H-PYRAZOLES

ABSTRACT OF THE DISCLOSURE

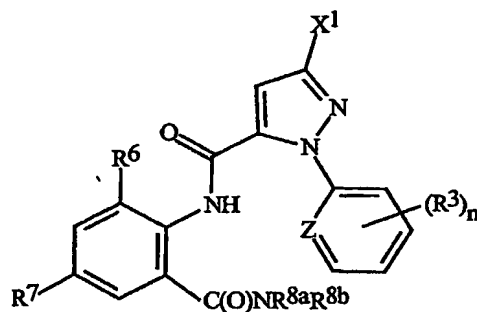
This invention relates to a method for preparing a 3-halo-4,5-dihydro-1H-pyrazole  
5 compound of Formula I

**I**

comprising contacting with  $HX^1$  a different 4,5-dihydro-1H-pyrazole compound of Formula  
II

**II**

10 wherein  $X^1$  is halogen and L, R, k and  $X^2$  are as defined in the disclosure. This invention  
also discloses preparation of compounds of Formula III

**III**

wherein  $X^1$ ,  $R^3$ ,  $R^6$ ,  $R^7$ ,  $R^{8a}$ ,  $R^{8b}$  and n are as defined in the disclosure.

4.

7



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